ATTEMPTING TO MAINTAIN NORMOGLYCEMIA DURING CARDIOPULMONARY BYPASS WITH INSULIN MAY INITIATE POST-OPERATIVE HYPOGLYCEMIA.

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ABSTRACT

Cardiopulmonary bypass is known to cause alterations in insulin secretion and resistance, resulting in profound hyperglycemia. Aggressive treatment of the resulting hyperglycemia intra-operatively could result in a severe degree of post-operative hypoglycemia. We undertook this prospective non-randomized clinical study to compare the alterations in glucose homeostasis in diabetic (group A, n=50) and non-diabetic (Group B, n=50) patients undergoing moderate hypothermic (30°C) cardiopulmonary bypass for coronary artery bypass grafting (CABG). All patients had a fasting blood sugar level done on the morning of surgery. Blood sugars were monitored intra-operatively and post-operatively at fixed time intervals. Intra-operative hyperglycemia was treated aggressively by a continuous infusion of injecting plain insulin. Both the groups experienced similar significant increase in blood glucose levels during bypass ($p=0.00003$). However, the mean blood glucose level upon arrival in the intensive care unit was significantly decreased in group B compared to group A ($p=0.0002$). 60% of group B and 10% of group A patients required treatment for post-operative hypoglycemia (blood glucose level $<60\text{mg/dl}$). This clinical study reveals that attempting to maintain normoglycemia in this setting with Insulin may initiate post-operative hypoglycemia.

KEY WORDS

Insulin, blood glucose levels, cardiopulmonary bypass.

INTRODUCTION

In patients undergoing cardiac surgery, cardiopulmonary bypass (CPB) induces alterations in insulin secretion, resistance and profound hyperglycemia. This phenomenon has been explained by an increased hepatic glucose production, insufficient insulin release, decreased glucose clearance and decreased glucose utilization during CPB (1). Hyperglycemia has been shown to worsen neurologic injury, probably because of anaerobic glycolysis induced conversion of glucose to lactate, which causes intra-cellular acidosis and impairment of cellular metabolism (2,3). Anesthesia, surgical stress, total body perfusion and composition of the priming fluid are all factors that effect glucose and insulin metabolism without

any major change in body temperature during CPB.

Since hypothermia is used to lower cardiac and general metabolism during cardiac surgery, we investigated its impact by comparing the alterations in glucose homeostasis in diabetic and non-diabetic patients undergoing moderate hypothermic cardiopulmonary bypass for coronary artery bypass grafting (CABG).

MATERIALS AND METHODS

In this prospective non-randomized clinical study we divided our subjects into two groups. Group A comprised of 50 diabetic patients who were on pre-operative insulin therapy and Group B comprised of 50 non-diabetic patients. Patients requiring pre-operative inotropic drugs, intra-aortic balloon pump support or mechanical ventilatory support were not included in the study. Any patient exhibiting significant pulmonary, endocrine, metabolic or neurologic pathology, any patients who developed intra-operative hypoglycemia and needed correction with dextrose infusions and patients who developed

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a low cardiac output at the time of weaning off bypass and required the use of inotropic support in excess of 5µg/kg/min of injection dopamine or the use of a mechanical support in the form of an intra-aortic balloon pump were excluded from the study. Medications such as calcium channel blockers and beta-blockers were continued until the night before surgery. Nitrates were continued even on the morning of surgery. Anti platelet drugs were stopped a week before surgery. All the patients of Group A, all of whom were insulin dependent diabetics, did not receive any parenteral insulin before surgery. All the patients in both groups had a fasting blood glucose level done before surgery.

All the patients in both the study groups were pre-medicated on the night before and on the morning of surgery with Tab. Diazepam (0.2mg/kg) and Tab. Ranitidine (3mg/kg) orally. All patients were infused with 0.9% normal saline intravenously and received general anesthesia. The intra-operative anesthetic induction technique was the same in all patients and consisted of intravenous fentanyl 5µg/kg and midazolam 0.2mg/kg. and injection vecuronium bromide was used for muscle paralysis in a dose of 0.1mg/kg. The blood glucose level was estimated immediately after the intubation of the trachea. Anesthesia was maintained by the use of oxygen and nitrous oxide in a ratio of 40:60 and isoflurane was used in a concentration of 0.5-1.5%. Five minutes after sternotomy a blood glucose level was estimated in all the patients. Injection heparin was instituted in a dose of 300 IU/kg intravenously to achieve total body heparinization towards preparation for going onto cardiopulmonary bypass (CPB). Ringers lactate was used as the pump prime solution, the constituents of which are outlined in Table 1. Once the patient was put on CPB and full non-pulsatile bypass flows of 2.2L/ m² body surface area/min was achieved, the aorta was cross clamped and a blood sugar level was estimated. The perfusionist maintained a perfusion pressure of 50-60 mm Hg injection midazolam and injection vecuronium bromide were given in a dose of 0.1mg/kg and 0.05 mg/kg injection fentanyl was infused in dose of 0.01µg/kg/min by the help of a syringe pump into the venous reservoir of the bypass machine. At this stage of the operation injection plain insulin was infused into the venous reservoir of the bypass machine by the use of an infusion pump to maintain a blood glucose level between 120-150mg/dl in both the study groups. During the conduct of cardiopulmonary bypass blood glucose levels were

estimated every 15 minutes in both the study groups. After the surgical procedure was completed on bypass the patient was gradually rewarmed to 38°C by the use of the haemotherm. Alpha stat blood gas management was used in all patients. Separation from CPB was facilitated by intra-venous inotropic drugs (injection dopamine in a dose of 5µg/kg/min) used at the discretion of the anesthetist. At this stage of the study the insulin infusion was discontinued. Injection midazolam was administered in a dose of 0.1mg/kg and the fentanyl infusion was continued intravenously. After successful weaning off CPB and achieving stable haemodynamics for 15 minutes a blood glucose level was estimated. The action of heparin was reversed with a calculated dose of injection protamine sulphate. Again, no dextrose containing fluids were infused. Injection nitroglycerine was used in a dose of 0.2-0.5 mg/kg/min for blood pressure control if needed. The surgical incision was closed in layers, and during the period of sternal wiring a blood glucose level was estimated. After completion of the operation, patients were transferred to the intensive care unit. In the intensive care unit blood glucose levels were estimated every half hourly till the patient was extubated. Tracheal extubation was accomplished at the earliest clinically appropriate time. The infusion of injection fentanyl was discontinued prior to shifting the patient to the intensive care unit. Postoperative care was standardized for all patients.

Fisher's exact test was applied to categorical data. Student's t-test (two tailed) was used to test the difference between the means in the two groups. A 'p' value of <0.05 was considered statistically significant, and 'p' values are reported only when significance was found. Results are expressed as means ± standard deviation unless otherwise indicated.

RESULTS

Demographic and clinical characteristics of patients and the peri-operative data are presented in tables 2 and 3 respectively. In both the groups of patients we were able to achieve normoglycemia with the study protocol. Group A (diabetic) patients received 68 ± 12 units of insulin and group B (non diabetic) patients received 59 ± 14 units of insulin. Table 4 presents peri-operative blood glucose levels for both groups. Although both the groups experienced significant increase in blood glucose levels during CPB as compared to the baseline levels

($p=0.00003$), there was no difference between the groups. However, the mean blood glucose level after arrival in the intensive care unit was significantly decreased in group B ($p=0.0002$) as compared to group A. 60% of group B and 10% of group A patients required treatment for post-operative hypoglycemia (blood glucose level $<60\text{mg/dl}$).

All patients in both groups had an uneventful intra-operative course. No patients in both the groups had any rhythm disturbances or myocardial infarction in the peri-operative period. There was no morbidity or mortality encountered in both the study groups. All patients in both the groups were eventually discharged uneventfully from the hospital.

DISCUSSION

This study revealed that "tight control" of intra-operative blood glucose was attainable in diabetic and non diabetic patients undergoing elective CABG under moderate hypothermic conditions. Furthermore 60% of non diabetic patients and 10% of diabetic patients required treatment for post-operative hypoglycemia (blood glucose $<60\text{mg/dl}$). These results indicate that attempting to maintain normoglycemia in this setting may initiate post-operative hypoglycemia.

The appropriate intra-operative management of hyperglycemia during cardiac surgery remains controversial (4-8). One study demonstrated that peri-operative hyperglycemia actually benefited patients undergoing cardiac surgery by decreasing peri-operative fluid requirements and thus decreasing postoperative fluid retention (7). However other investigations indicate that hyperglycemia during hypothermic circulatory arrest (9,10) or during normothermic CPB (11) may contribute to neurological dysfunction. Although not extensively studied, the likely causes of hyperglycemia during and after CPB include decreased insulin secretion and peripheral glucose utilization (hypothermia and pancreatic hypoperfusion) and/or increased activity of insulin antagonists (glucagon, epinephrine, norepinephrine, growth hormone and cortisol) (12).

In a clinical study published previously by Kuntschen *et al* (13) described the factors influencing glucose and insulin metabolism during CPB. They described that anesthesia, surgical trauma and the perfusion procedure lead to the release of stress hormones, inhibit glucose utilization by peripheral tissues and stimulate endogenous glucose production without

a corresponding increase in endogenous insulin release. Hypothermia brings an additional element of metabolic complexity. The study done by Kuntschen *et al* concluded that with hypothermia there is an actual decrease in plasma insulin levels that persists throughout and after CPB (1). They also concluded that there is no relationship between the magnitude of the glucose load and insulin response in hypothermic patients. Inhibition of insulin secretion by hypothermia has also been reported by other clinical trials (14-16).

We were able to attain normoglycemia in both the groups. Both groups experienced similar significant increases in blood glucose levels during CPB. After CPB, blood glucose levels returned towards pre-CPB values. This observation suggests that the under perfusion of the peripheral muscle mass, may be associated with decreased glucose utilization during CPB (1). A glucose load in the priming fluid of the bypass circuit leads to marked hyperglycemia. In our study the priming fluid used was ringers lactate solution. The lactate gets converted to glucose through the Cori's cycle in the liver (17). After an initial blood glucose peak, which reflects primarily a dilution effect, the slow return towards baseline values (which are not yet reached by the end of the operation) signals decreased glucose assimilation under hypothermic conditions. Kuntschen *et al* have demonstrated that the slope of glucose correction is initially faster during hypothermia but the clearance is slower during the rewarming phase (1). For the initial period of perfusion this can be explained by suppression of hepatic glucose production in hypothermia. Altogether, the sluggishness of glucose clearance mechanism involves interaction of impaired insulin secretion, reduced insulin sensitivity and incomplete suppression of endogenous glucose production. As a result, the assimilation of exogenous glucose during CPB necessitates the infusion of large doses of insulin (18).

CONCLUSION

In conclusion, hypothermic cardiopulmonary bypass causes significant alterations in glucose and insulin metabolisms during cardiac surgery. Hypothermia inhibits insulin secretion and glucose production, which are later revived during the period of rewarming. During CPB, the metabolic state of a non-diabetic subject is not very different from that of a diabetic. This study revealed that adequate control of intra-

operative blood glucose levels was attainable in both the study groups undergoing CABG under hypothermic conditions. Furthermore, 60 % of non-diabetic patients and 10% of diabetic patients required treatment for postoperative hypoglycemia (< 60 mg/dL). These results indicate that attempting to maintain normoglycemia in this setting with insulin may initiate postoperative hypoglycemia.

ACKNOWLEDGEMENTS

We would like to place on record our gratitude to the members of the Department of Clinical Biochemistry, St. John's Medical College Hospital Bangalore for their assistance in the completion of this study.

Table 1
Concentration of ions in the prime fluid.

Strong Ion	meq/l
Sodium	131
Potassium	5
Chloride	111
Calcium	4
Bicarbonate (as lactate)	29

meq/l: Milli-equivalents per liter.

Table 2
Demographic and Clinical Characteristics of patients.

	Group A (n=50)	Group B (n=50)	'p' value
<u>Patient Data:</u>			
Age (years):	64±14	61±11	NS
Male patients:	27	29	NS
Female patients:	23	21	NS
Height (cm):	176±7	168±9	0.004
Weight (Kg):	78±11	72±10	NS
<u>Pre-operative medications:</u>			
Beta blockers:	34	36	NS
Calcium channel blockers:	27	21	NS
Nitrates:	43	45	NS
ACE Inhibitors:	11	7	NS
Digoxin:	1	3	NS
Diuretics:	14	17	NS

Results are expressed as mean ± standard deviation.

ACE: Angiotensin converting enzyme.

NS: Not significant.

Table 3
Peri-operative patient data.

	Group A	Group B	'p' value
<u>Anesthetic drugs:</u>			
Total fentanyl (µg/kg)	26±1.4	27±0.8	NS
Total midazolam (µg/kg)	180±52	184±41	NS
Total vecuronium (µg/kg)	584±68	596±78	NS
<u>Before Cardiopulmonary bypass:</u>			
Isoflurane use	50	50	NS
Nitroglycerine use	50	50	NS
<u>During cardiopulmonary bypass:</u>			
Lowest temperature (°C)	28.0±0.0	28.2±0.4	NS
Total bypass time (min)	130±22	128±28	NS
Aortic cross clamp time (min)	86.2±14.2	88.4±11.4	NS
Total insulin dose (units)	68±12	59±14	NS
<u>After cardiopulmonary bypass:</u>			
Use of inotropes	50	50	NS
Nitroglycerine use	50	50	NS
Isoflurane use	11	14	NS
<u>Surgical data:</u>			
Total grafts put	3.2 ±0.4	3.6±0.2	NS

Results are expressed as mean ± standard deviation.

NS: Not significant.

Table 4

Peri-operative blood glucose levels during various stages of the surgery.

	Group A	Group B	'p' value
<u>Morning of surgery (6am):</u>			
Baseline (mg/dl)	106.5±14.2	98.4±8.4	NS
<u>Pre CPB:</u>			
Post intubation (mg/dl)	104.8±11.6	92.6±7.8	NS
Post sternotomy (mg/dl)	108.6±10.4	95.6±8.2	NS
<u>On CPB:</u>			
Aorta cross clamped (mg/dl)	168±14.2	172±12.4	NS
<u>On insulin infusion:</u>			
Mean value on CPB (mg/dl)	138±11.6	141±8.8	NS
<u>Post CPB, and off insulin infusion:</u>			
15 minutes off CPB (mg/dl)	141±9.4	145±9.2	NS
Sternal wiring (mg/dl)	110±7.8	108±8.6	NS
<u>In the ICU:</u>			
Mean value in the ICU (mg/dl)	98.2±38.6	81.8±39.8	0.0002

All values are expressed as mean ± standard deviation.

CPB: Cardiopulmonary bypass.

ICU: Intensive care unit.

NS: Not significant.

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